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Annulative Synthesis of Thiazoles and Oxazoles from Alkenyl Sulfoxides and Nitriles via Additive Pummerer Reaction

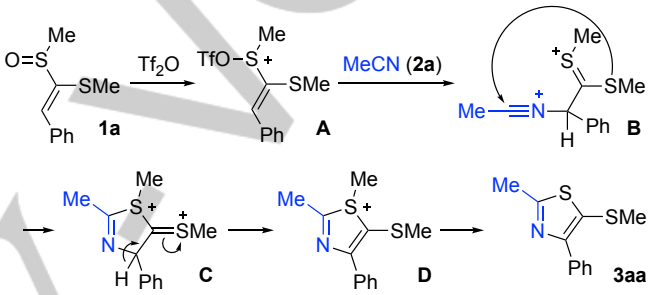
Mitsuki Hori, Keisuke Nogi, Aiichiro Nagaki, and Hideki Yorimitsu*

Abstract: Pummerer-based annulation of alkenyl sulfoxides, mainly ketene dithioacetal monoxides (KDMs), with nitriles has been developed. By means of trifluoromethanesulfonic anhydride (Tf_2O) as an activator, additive Pummerer reaction and subsequent C–S-bond-forming cyclization from the nitrilium intermediates furnished the corresponding thiazoles. Moreover, the nitrilium intermediates proved to be interrupted intermolecularly by H_2O to afford oxazoles instead of thiazoles.

The Pummerer reaction is a unique transformation of sulfoxides, and has been recognized as a powerful and attractive method in organic synthesis.[1] Besides classical Pummerer reactions of alkyl sulfoxides, transformations of aryl and alkenyl sulfoxides, called extended Pummerer reactions, have been actively investigated over the last two decades.[2]

Recently, we have been interested in Pummerer-based transformations of alkenyl sulfoxides including ketene dithioacetal monoxides (KDMs).[2e,h,3] To develop new Pummerer-based transformation of KDMs, we conducted the reaction of KDM **1a** with a series of nucleophiles. During the course of the investigation, we accidentally found that 5-(methylsulfanyl)thiazole **3aa** was obtained when **1a** and trifluoromethanesulfonic anhydride (Tf_2O) were mixed in acetonitrile (**2a**) as a solvent (Scheme 1). The reaction would be initiated by activation of KDM **1a** with Tf_2O to generate sulfonium **A**. Subsequent additive Pummerer-type reaction,[2a–d] in which the nitrogen atom of acetonitrile undergoes S_N2'-type reaction, would afford intermediate **B**. Following C–S-bond-forming cyclization, and deprotonation would afford *S*-methylthiazolium **D**. Finally, demethylation of **D** would provide thiazole **3aa**.[4]

The reaction of nitriles under Pummerer conditions was first reported by Vanker.[5] In that report, Ritter-type addition of nitriles to the α-position of alkyl sulfoxides took place and subsequent hydrolysis afforded α-amidoalkyl sulfides as products. Very recently, Peng reported the reactions of aryl sulfoxides with alkanenitriles under Pummerer conditions.[6] In these cases, interrupted Pummerer reaction proceeded, in which the nitrogen atom attacked onto the sulfur atom to construct an S–N bond, instead of additive Pummerer reaction. The following [3,3] sigmatropic rearrangement produced *ortho*-cyanoalkylation products. To the best of our knowledge, additive Pummerer reaction with nitriles has never been reported.



Scheme 1. Possible reaction mechanism for formation of thiazole **3aa**.

Thiazoles represent an important structural motif in various functional molecules including biologically active compounds[7] and functional materials.[8] Although a number of methodologies for the synthesis of thiazoles have been established,[9,10] we expected that the development of a new route to thiazoles from readily accessible alkenyl sulfoxides and nitriles would be valuable. With these considerations in mind, here we report annulative synthesis of thiazoles via additive Pummerer reaction of alkenyl sulfoxides with alkane- and arenenitriles. Moreover, we found that interception of nitrilium intermediate of the type **B** by H_2O intermolecularly provided the corresponding oxazoles instead of thiazoles.

Optimization study for the synthesis of **3aa** is summarized in Table 1. The reaction of **1a** with 192 equivalents of acetonitrile in the presence of 1.0 equivalent of Tf_2O afforded a 53% yield of **3aa** (entry 1). Increasing the concentration of **1a** as high as 0.2 M improved the yield of **3aa** to 62% while the higher concentration of **1a** (0.4 M) slightly decreased the yield (entries 2 and 3). Although a 58% yield of **3aa** was obtained when the reaction was conducted with 48 equivalents of **2a** using $MeNO_2$ as a co-solvent, the use of 10 equivalents of **2a** significantly diminished the yield of **3aa** to 28% (entries 4 and 5). By means of 1.5 equivalents of Tf_2O and 96 equivalents of acetonitrile as a single solvent, **3aa** was obtained in 77% yield and was isolated in 75% yield (entry 6).

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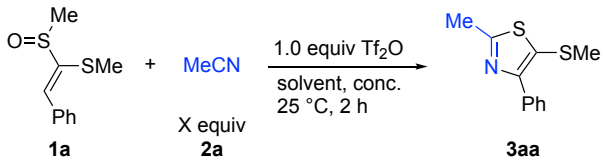
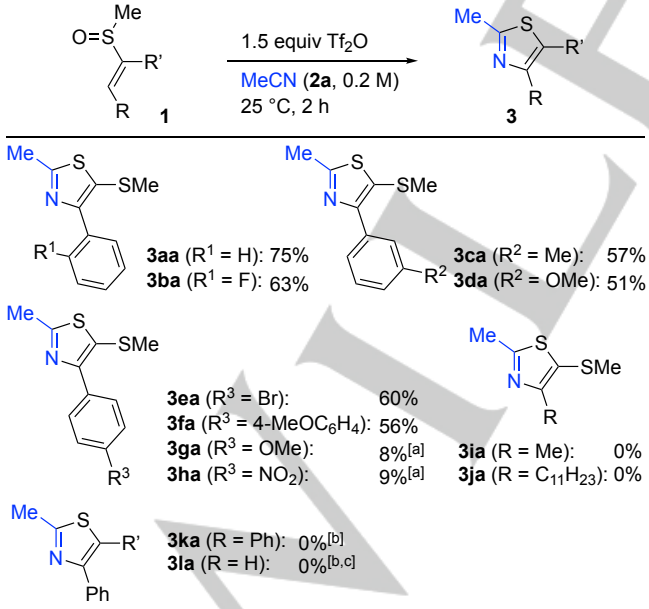
Table 1. Condition screenings.



entry	X (equiv)	solvent	conc. (M)	NMR yield (%)
1	192	neat	0.1	53
2	96	neat	0.2	62
3	48	neat	0.4	56
4	48	$MeNO_2$	0.2	58
5	10	$MeNO_2$	0.2	28
6[a]	96	neat	0.2	77 (75)[b]

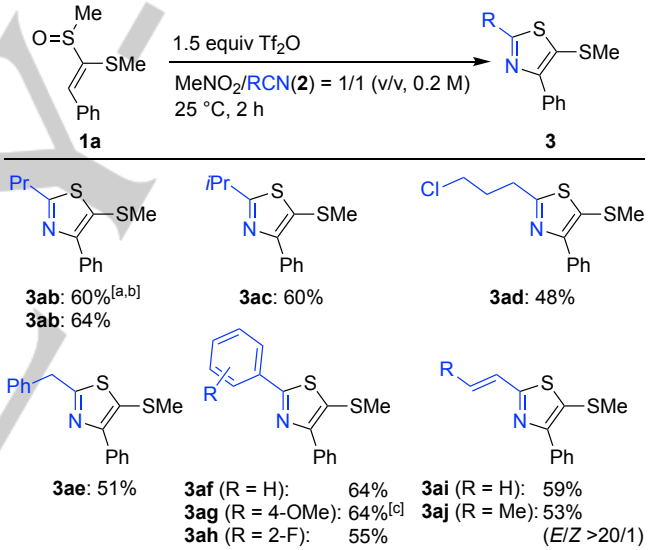
[a] 1.5 equiv of Tf_2O. [b] Isolated yield.

The scope of the reaction with respect to KDMs is shown in Scheme 2. KDMs having electronically neutral aryl rings at the β-position were applicable to the reaction to afford thiazoles **3ba**–**3fa** in moderate yields. On the other hand, considerably electron-donating and -withdrawing 4-methoxphenyl and 4-nitrophenyl groups proved to be not suitable. The desired products, **3ga** and **3ha**, were obtained in less than 10% yields while the KDMs were completely consumed. β-Alkyl substituted KDMs, **1i** and **1j**, gave complex product mixtures. The sulfanyl moiety at the α-position was crucial for the reaction, and α-phenyl and α-unsubstituted alkenyl sulfoxides **1k** and **1l** also afforded complex product mixtures.



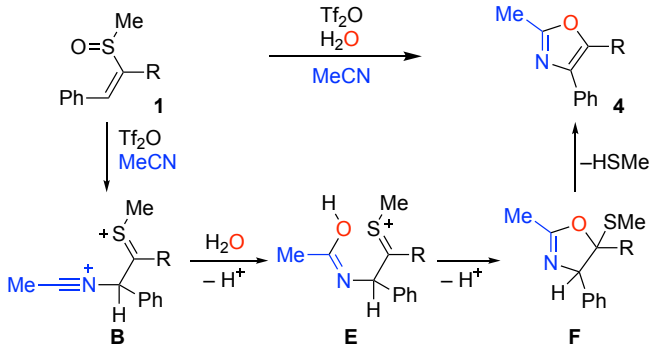
Scheme 2. Scope of KDMs. [a] NMR yield. [b] At 0 °C. [c] Dodecyl 2-phenylvinyl sulfoxide (**1l**) was used.

Next, we investigated the scope with respect to nitriles (Scheme 3). Instead of **2a**, butyronitrile (**2b**) also participated in the reaction. In this case, the use of $MeNO_2$ as a co-solvent slightly improved the yield of **3ab** to 64%. Therefore, we decided to use the co-solvent system ($MeNO_2$/nitrile **2** = 1/1, v/v) for exploring the scope with respect to nitriles. As a secondary alkanenitrile, isobutyronitrile (**2c**) was converted to the corresponding thiazole **3ac** in 60% yield. The use of 4-chlorobutyronitrile (**2d**) also afforded the desired product **3ad** in 48% yield. Phenylacetonitrile (**2e**) smoothly underwent the present transformation affording benzyl-substituted thiazole **3ae** in a moderate yield. Fortunately, arenenitriles were also found to be applicable. The reaction of **1a** with benzonitrile (**2f**) furnished the corresponding thiazole **3af** in 64% yield. Electron-rich 4-methoxybenzonitrile (**2g**) promptly reacted with **1a** to afford **3ag** in 64% yield even though the amount of **2g** was reduced to 3.0 equivalents. Although the employment of 2-methoxybenzonitrile resulted in a low yield of the product probably due to its steric hindrance, sterically less hindered 2-fluorobenzonitrile (**2h**) was involved in the reaction to afford **3ah** in 55% yield. Gratifyingly, the reaction of acrylonitrile (**2i**) and *trans*-crotononitrile (**2j**) furnished desired products **3ai** and **3aj** in moderate yields without deterioration of their C–C double bonds.



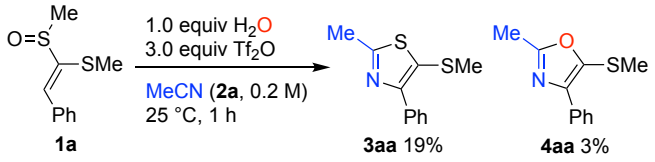
Scheme 3. Scope of nitriles. [a] Without $MeNO_2$. **2b** was used as a solvent. [b] NMR yield. [c] 3.0 equiv of **2g**, 3.0 equiv of Tf_2O, for 0.5 h.

In view of the reaction mechanism of the thiazole synthesis, we conceived that the intermediate like **B** generated via additive Pummerer-type reaction could be led to the corresponding oxazoles by the addition of water as an oxygen source (Scheme 4). We expected that nucleophilic attack of H_2O to nitrilium **B** would afford thionium species **E**, and subsequent C–O-bond-forming cyclization and departure of methanethiol from **F** would provide oxazoles **4**. Actually, in most reactions in Scheme 3, 5-(methylsulfanyl)oxazoles were observed in around 5% yields because of a trace amount of water present in the reaction mixture. These observations encouraged us to explore the synthesis of oxazole.

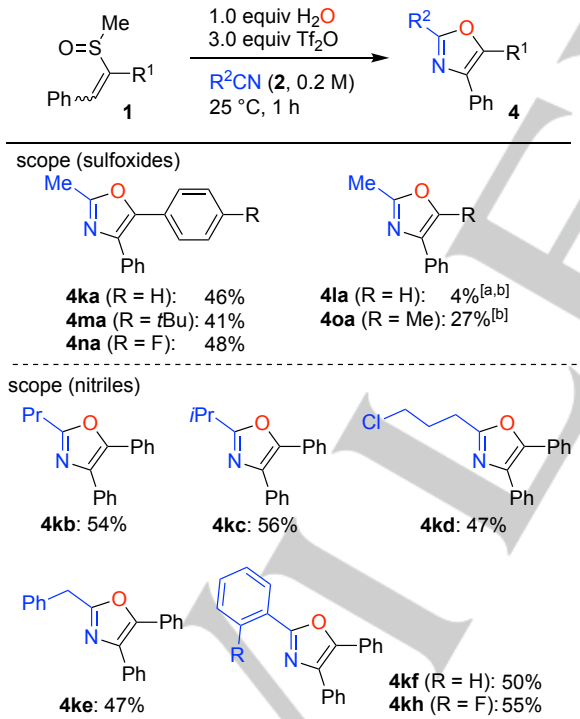


Scheme 4. Synthesis of oxazoles from alkenyl sulfoxides.

We first tired the reaction of KDM **1a** with acetonitrile in the presence of Tf_2O and 1.0 equivalent of H_2O. However, thiazole **3aa** was still preferentially obtained and the yield of oxazole **4aa** was only 3% (Scheme 5).



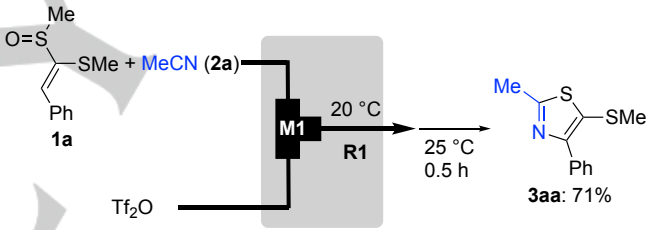
Scheme 5. Attempted synthesis of oxazole from KDM **1a**.



Scheme 6. Scope of the synthesis of oxazoles **4**. [a] Dodecyl 2-phenylvinyl sulfoxide (**1l**) was used. [b] NMR yield.

To suppress the C–S-bond formation (**B** to **C** in Scheme 1), α-phenyl-substituted alkenyl sulfoxide **1k** was used as a substrate. As a result, desired oxazole **4ka** was obtained in 46% yield in the presence of 3.0 equivalents of Tf_2O and 1.0 equivalent of H_2O (Scheme 6). Although 4-*tert*-butylphenyl- and 4-fluorophenyl-substituted alkenyl sulfoxides **1m** and **1n** underwent the reaction, α-unsubstituted alkenyl sulfoxide **1l** was not applicable to afford a complex mixture. A methyl substituent at the α-position also diminished the yield of oxazole **4oa**. Compared to the synthesis of thiazole shown in Schemes 2 and 3, the reaction efficiency was low and nitriles should be used as the solvent. However, both of alkane- and arenenitriles furnished the corresponding oxazoles **4kb**–**4kf** and **4kh** in moderate yields.

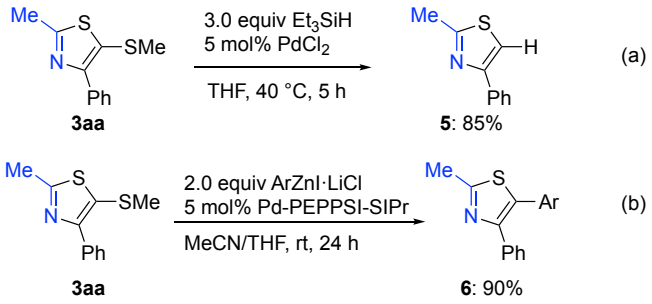
Next, we attempted the synthesis of thiazoles **3** in a larger scale. However, the reaction with 1 mmol of **1a** afforded much less yield of **3aa** as low as 55% (75% yield with 0.2 mmol of **1a**, Scheme 2). We inferred that the efficiency of mixing of the substrates and Tf_2O would be problematic in scaled-up experiments in batch reactors. We thus turned our attention to the use of flow microreactors that enables extremely fast mixing by virtue of the short diffusion path.[11] The setup to realize the synthesis of **3aa** is shown in Figure 1, consisting of a T-shape micromixer (**M1**) and a microtube reactor (**R1**). Solutions of KDM **1a** in acetonitrile (**2a**) and Tf_2O in CH_2Cl_2 were mixed together in **M1** and reacted in **R1** for 2.0 s. The resulting mixture was collected in a flask, allowed to stand at room temperature for 0.5 h, and treated with alumina for neutralization. As a result, we successfully obtained **3aa** in 71% yield from 3.0 mmol of **1a**.



Flow conditions:
1a (0.1 M, 1.0 equiv), **2a** (192 equiv as solvent);
Tf_2O (0.1 M in CH_2Cl_2 1.0 equiv)

Figure 1. Large-scale synthesis in a flow microreactor.

To further demonstrate the utility of thiazoles **3** obtained, we subjected thiazole **3aa** to transformations of the C–SMe bond. Hydrogenative removal of the methylsulfanyl moiety according to Nakada's protocol[12] uneventfully proceeded to afford 2-methyl-5-phenyl-1,3-thiazole (**5**) in 85% yield. (Scheme 7a). We then tried arylation of **3aa** via C–S bond cleavage. In the presence of 5 mol% of Pd-PEPPSI-SIPr, Negishi-type arylation with an arylzinc reagent smoothly proceeded to afford the corresponding 5-arylthiazole **6** in 90% yield (Scheme 7b).[13]



Scheme 7. Exocyclic C–S-cleaving transformations of thiazole **3aa**. Ar = 4-$EtO_2CC_6H_4$.

In conclusion, we have developed the annulative synthesis of 5-(methylsulfanyl)thiazoles from KDMs and nitriles via additive Pummerer reaction. Moreover, the reaction pathway can be switched to the formation of oxazoles by adding H_2O as the oxygen source.

Acknowledgements

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Keywords: additive Pummerer reaction• Ritter-type reaction• alkenyl sulfoxide• thiazole • oxazole

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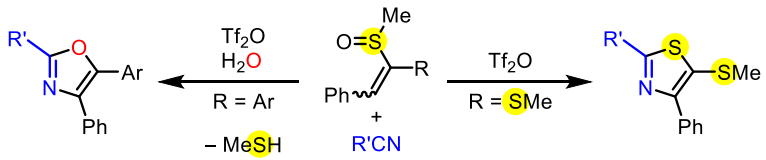

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